UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/744,748	01/29/2001	Hisashi Narimatsu	1241.17	4282

7590 08/18/2003

Fitzpatrick Cella Harper & Scinto
30 Rockefeller Plaza
New York, NY 10112-3801

EXAMINER	
RAO, MANJUNATH N	
ART UNIT	**PAPER NUMBER**
1652	14

DATE MAILED: 08/18/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/744,748	NARIMATSU ET AL.	
	Examiner	Art Unit	
	Manjunath N. Rao, Ph.D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-75* is/are pending in the application.

4a) Of the above claim(s) *19-23,25-50 and 54-75* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18,24 and 51-53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *11* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claims 1-75 are currently pending in this application. Claims 1-18, 24, 51-53 are now under consideration. Claims 19-23, 25-50, 54-75 remain withdrawn from consideration as being drawn to non-elected invention.

Applicants' amendments and arguments filed on 6-6-03, paper No.12, have been fully considered and are deemed to be persuasive to overcome the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1 and claims 3-18, 24, 51-53 which depend therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 recites the phrase "derived from mouse or human cells". The metes and bounds of this phrase is not clear to the Examiner. Literally, while the term "derived" means "to isolate from or obtain from a source", the above term could also mean "to arrive at by reasoning i.e., to deduce or infer" or also mean "to produce or obtain from another substance". Therefore, it is not clear to the Examiner either from the specification or from the claims as to what applicants mean by the above phrase. It is not clear to the Examiner whether the polypeptides "derived from mouse or human cells" encompasses specific polypeptides as in "derived from SEQ ID NO:1 or 2" or whether it encompasses recombinants, variants and mutants of any polypeptide from any source and

labeled as "derived from mouse or human cells". As applicants have not provided a definition for the above phrase, Examiner has interpreted the claims broadly to mean, that a "derived from mouse or human cells" polypeptides encompasses sequences which are recombinants, variants, or mutants of any fucosyltransferase. Examiner has given the same interpretation while considering the claims for all other rejections.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-18, 24, 51-53 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an enzyme with SEQ ID NO:1 or 2 having the activity of transferring fucose to an N-acetylglucosamine structure in an N-acetyllactosamine structure existing in a nonreducing terminus of a sugar chain via an alpha 1,3-linkage, but not having a similar activity to transfer fucose to N-acetylglucosamine residue in an alpha 2,3-sialyl N-acetyllactosamine structure, encoded by the polynucleotide with SEQ ID NO:3, 4, or 5, does not reasonably provide enablement for all such enzymes derived from mouse or human cells (see above for interpretation of "derived from" phrase). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3)

the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 1, 3-18, 24, 51-53 are so broad as to encompass any alpha 1,3-fucosyltransferase isolated from any source including variants, mutants and recombinants that selectively fucosylates N-acetylglucosamine via alpha 1,3-linkage. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of such enzymes broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the nucleotide and encoded amino acid sequence of only a single human alpha 1,3-fucosyltransferase.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications and fragments of any alpha 1,3-fucosyltransfaase that exhibits the selective property described above because the specification does not establish: (A) regions of the protein structure which may be modified without effecting such activity; (B) the general tolerance of such alpha 1,3-fucosyltransferases to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any alpha 1,3-fucosyltransferase residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any or all such alpha 1,3,-fucosyltransferase or such enzymes with an enormous number of amino acid modifications. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of alpha 1,3-fucosyltransferases having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

In response to the previous Office action applicants have traversed the above rejection arguing that the specification teaches all the requisite information and in addition provides polypeptide and DNA from mouse and humans and those ordinarily skilled in the art can produce the variant of the claimed enzyme according to the method described in the application

and that the scope of the claims is entirely commensurate with the disclosure. Examiner respectfully disagrees. Even though applicants have made an attempt to limit the claim to polypeptides of mouse and humans the claim language tends to be much broader. Furthermore, it is not uncommon in humans and mouse to find isoforms of the same enzyme. Applicants arguments are not persuasive to overcome the above rejection because while methods to produce variants of a known sequence, such as site-specific mutagenesis, random mutagenesis, etc. are well known to the skilled artisan producing variants as claimed by applicants requires that one of ordinary skill in the art know or be provided with guidance for the selection of which of the infinite number of variants have the claimed property or guidance as to which specific amino acids in the amino acid sequence can be changed by way of addition, deletion, substitution without affecting the activity. Without such guidance one of ordinary skill would be reduced to the necessity of producing and testing all of the virtually infinite possibilities. This would clearly constitute undue experimentation. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Such guidance has not been provided in the instant specification. As previously stated the specification does not establish: (A) regions of the protein structure which may be modified without effecting activity; (B) the general tolerance of said polypeptides to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful. Therefore the above rejection is maintained.

Claims 1, 3-18, 24, 51-53 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1, 3-18, 24, 51-53 are directed to polypeptides having the activity of transferring fucose to an N-acetylglucosamine structure in an N-acetyllactosamine structure existing in a nonreducing terminus of a sugar chain via an alpha 1,3-linkage, but not having a similar activity to transfer fucose to N-acetylglucosamine residue in an alpha 2,3-sialyl N-acetyllactosamine structure. Claims 1, 3-18, 24, 51-53 are rejected under this section of 35 USC 112 because the claims are directed to a genus of polypeptides derived from SEQ ID NO:1 or 2 including modified polypeptide sequences, modified by at least one of deletion, addition, insertion and substitution of an amino acid and fragments that have not been disclosed in the specification. No description has been provided of all the polypeptide sequences encompassed by the claims. No information, beyond the characterization of SEQ ID NO:1 and 2 has been provided by applicants which would indicate that they had possession of the claimed genus of modified polypeptides. The specification does not contain any disclosure of the structure of polypeptide sequences derived from SEQ ID NO:1 or 2, including fragments and variants within the scope of the claimed genus. The genus of polypeptides claimed is a large variable genus including peptides which can have a wide variety of structures. Therefore many structurally unrelated polypeptides are encompassed within the scope of these claims. The specification discloses only a two species of the claimed genus which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one

skilled in the art cannot reasonably conclude that applicant had possession of the claimed invention at the time the instant application was filed.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Applicants have not responded to the above rejection. However, in view of the claim amendments, Examiner has withdrawn the rejection as it applied to claim 2, but continues to maintain the rejection as it applies to the remaining claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3, 12-18, 24, 53 are rejected under 35 U.S.C. 102(a) as being anticipated by Ge et al. (J. Biol. Chem. Vol., 272(34):21357-21363, Aug. 1997). This rejection is based upon the public availability of a printed publication. Claims 1, 3, 12-18, 24, 53 of the instant application is drawn to an enzyme having the activity of transferring fucose to an N-acetylglucosamine structure in an N-acetyllactosamine structure existing in a nonreducing terminus of a sugar chain via an alpha 1,3-linkage, but not having a similar activity to transfer fucose to N-acetylglucosamine residue in an alpha 2,3-sialyl N-acetyllactosamine structure

derived from mouse or humans. Claims are also drawn to method of making reaction products using such enzymes. Ge et al. disclose an enzyme with identical properties (see abstract and the entire publication), and method of making such polypeptides and use it in a reaction to make reaction products. Since claim 1 is directed to polypeptides *derived* from mouse or humans above claims read on the enzyme disclosed by Ge et al. Thus Ge et al. anticipate claims 1, 3, 12-18, 24, 53 of this application as written.

In response to the above rejection applicants argue that Ge et al. describes an enzyme derived from Helicobacter (as opposed to the derived from humans or mouse). Applicants also argue that Ge's US patent publication No. 2002/0068347 described an enzyme which also synthesizes the sugar chain having NeuAc α2-3Gal ß1-4GlcNAc (Fuc α1-3)structure existing in a non-reducing terminus. While this may be so, a perusal of the reference cited by the Examiner indicates no such information. Therefore unless applicants can show that the enzyme in the cited reference also has such a property (i.e., synthesizes the sugar chain having NeuAc α2-3Gal ß1-4GlcNAc (Fuc α1-3)structure existing in a non-reducing terminus), Examiner continues to maintain the above rejection.

Claims 1, 3, 12-18, 24, 53 are rejected under 35 U.S.C. 102(b) as being anticipated by Lowe et al. (J. Biol. Chem. Vol., 266(26):17467-17477, Sep. 1991). This rejection is based upon the public availability of a printed publication. Claims 1, 3, 12-18, 24, 53 of the instant application is drawn to an enzyme having the activity of transferring fucose to an N-acetylglucosamine structure in an N-acetyllactosamine structure existing in a non reducing terminus of a sugar chain via an alpha 1,3-linkage, but not having a similar activity to transfer

fucose to N-acetylglucosamine residue in an alpha 2,3-sialyl N-acetyllactosamine structure and enzymes derived from humans or mouse and methods of making such polypeptide by culturing said host cells. Claims are also drawn to method of making reaction products using such enzymes. Lowe et al. disclose an enzyme with identical properties (see abstract and the entire publication), method of making such polypeptides and use said polypeptide in a reaction to make reaction products. Since there the enzyme claimed is *derived* from humans and there is no limitation placed on the number of changes that can be present in the polypeptide, above claims read on the enzyme disclosed by Lowe et al. Thus Lowe et al. anticipate claims 1, 3, 12-18, 24, 53 of this application as written.

In response to the above rejection applicants argue that the enzyme of the application can synthesize the sugar chain having ß 1-4GlcNAc(Fuc α1-3) structure existing in a nonreducing terminus using a sugar chain having Gal ß 1-4GlcNAc structure as a substrate and at the same time it cannot synthesize the sugar chain having NeuAC α2-3Gal ß 1-4GlcNAc (Fuc α 1-3) structure using a sugar chain having α2-3Gal ß 1-4GlcNAc structure. In contrast to the above applicants argue that the enzyme described by Lowe's is a counter part of mouse Fuc-TIV which is unable to synthesize the oligosaccharide as above. In support of their argument applicants direct the Examiner's attention to the abstract of Lowe's reference and page 25048, left column lines 7-10. However, it appears that applicants are not referring to Examiner's reference but to some other reference of Lowe's et al. This is because the reference cited by the Examiner (J. Biol. Chem. Vol., 266(26):17467-17477, Sep. 1991) does not have page 25048 and nowhere in the reference said enzyme is referred to as Fuc-IV. On the contrary, the reference is drawn to a novel human fucosyltransferase which capable of efficiently utilizing N-acetyllactosamine to

form Galß1-4GlcNAc(Fuc α1→3) structure. Plainly, the polypeptide and the reference which applicants are referring to is not taught by Lowe et al. reference used by the Examiner.

Claims 1-9, 12, 17-18, 24, 51-53 are rejected under 35 U.S.C. 102(a) as being anticipated by Kaneko et al. (J. Biol. Chem. Vol., 272(34):21357-21363, Aug. 1997, in IDS paper No.6) or Kudo et al. (JBC, Oct 1998, Vol. 273:26729-38 in IDS paper No.6). This rejection is based upon the public availability of a printed publication. Claims 1-9, 12, 17-18, 24, 51-53 of the instant application is drawn to an enzyme isolated from humans or mice and having the amino acid sequence SEQ ID NO:1 or 2 and having the activity of transferring fucose to an N-acetylglucosamine structure in an N-acetyllactosamine structure existing in a non-reducing terminus of a sugar chain via an alpha 1,3-linkage, but not having a similar activity to transfer fucose to N-acetylglucosamine residue in an alpha 2,3-sialyl N-acetyllactosamine structure, wherein said enzymes are encoded by a polynucleotide which hybridizes under stringent conditions (as described in claim 2) to SEQ ID NO:2, 3 or 5, polynucleotides encoding such enzymes, vectors and host cells (transformants) including *E.coli* cells comprising such polynucleotides and methods of making such polypeptide by culturing said host cells. Claims are also drawn to method of making reaction products using such enzymes. Kaneko et al. and Kudo et al. disclose polypeptides which are 100% identical with SEQ ID NO:1 and 2 respectively and identical properties (see abstract and the entire publication), polynucleotide which encodes such enzymes, vectors and transformants comprising such polynucleotides and method of making such polypeptides and use it in a reaction to make reaction products. Thus

Kudo et al. or Kaneko et al. anticipate claims 1-9, 12, 17-18, 24, 51-53 of this application as written.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 10-11, 13-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Kudo et al. or Kaneko et al. as applied to claims 1-9, 12, 17-18, 24, 51-53 above, and further in view of the high level of knowledge in the art of molecular biology. Claims 10-11, 13-16 in this instant application are drawn to transformants wherein the transformants are specific animal cells or insect cells and to method for producing the polypeptide by using the milk of a transgenic animal or the plant parts of a transgenic plant or an in vitro method of translation wherein the DNA encoding the polypeptide is translated using an in vitro translation system. The references of Kudos et al. or Kaneko et al. have already been discussed above. While both the above references teach the polypeptide, polynucleotide, vector and a transformant and a method of making the polypeptide by culturing the transformant, the above references however do not teach the specific host cells for transformation or the transgenic plant or the animal and method of producing the polypeptide using the part of the plant or the milk of the animal or the in vitro method of translation as claimed in the above claims.

With the above two references in hand, it would have been obvious to one of ordinary skill in the art to choose any of the above cells for transformation or produce the polypeptide by

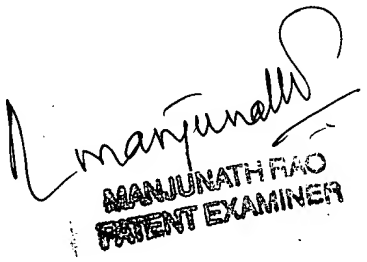
use of transgenic plants or animals since such techniques are well known in the art and are routinely used for bulk preparation of the heterologous polypeptides. One of ordinary skill in the art would have been motivated to do so because the polypeptide having the above activity has been recognized in the art as useful in preparation of specific carbohydrate structures which has applications in diagnosis of certain human disorders. One of ordinary skill in the art would have a reasonable expectation of success because the above references provide the purified polynucleotide expressing the above polypeptide and the art is rich in several of the techniques to perform the above experiments and also provides step by step guidance.

Therefore the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art.

Applicants have not responded to the above rejection in their response to the previous Office action.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Manjunath Rao whose telephone number is (703) 306-5681. The Examiner can normally be reached on M-F from 6:30 a.m. to 3:00 p.m. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, P.Achutamurthy, can be reached on (703) 308-3804. The fax number for Official Papers to Technology Center 1600 is (703) 305-3014. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.



Manjunath N. Rao Ph.D.
8/14/03